DNA shuffling of adeno-associated virus yields functionally diverse viral progeny.

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Public Summary:

Scientific Abstract:
Adeno-associated virus (AAV) vectors are extremely effective gene-delivery vehicles for a broad range of applications. However, the therapeutic efficacy of these and other vectors is currently limited by barriers to safe, efficient gene delivery, including pre-existing antiviral immunity, and infection of off-target cells. Recently, we have implemented directed evolution of AAV, involving the generation of randomly mutagenized viral libraries based on serotype 2 and high-throughput selection, to engineer enhanced viral vectors. Here, we significantly extend this capability by performing high-efficiency in vitro recombination to create a large (10(7)), diverse library of random chimeras of numerous parent AAV serotypes (AAV1, 2, 4-6, 8, and 9). In order to analyze the extent to which such highly chimeric viruses can be viable, we selected the library for efficient viral packaging and infection, and successfully recovered numerous novel chimeras. These new viruses exhibited a broad range of cell tropism both in vitro and in vivo and enhanced resistance to human intravenous immunoglobulin (IVIG), highlighting numerous functional differences between these chimeras and their parent serotypes. Thus, directed evolution can potentially yield unlimited numbers of new AAV variants with novel gene-delivery properties, and subsequent analysis of these variants can further extend basic knowledge of AAV biology.